a) a fragment of cell surface P95/nucleolin produced by chemical synthesis or recombinant techniques;

b) a pseudopeptide homologous to a fragment of cell surface P95/nucleolin produced by chemical synthesis or recombinant techniques.

IN THE DRAWINGS:

Subject to the approval of the Examiner, please replace the previously filed formal drawing of Figure 49 with a new drawing of Figure 49, 17 pages, attached hereto.

REMARKS

Formal Matters

Claims 1, 2, and 4-24 are pending in this application. Claims 1, 7, 8, 11, 12, and 14-23 have been withdrawn from consideration and claims 2, 4-6, 9, 10, 13, and 24 have been rejected by the Examiner. Applicants thank the Examiner for withdrawing many of the rejections, including ones directed to enablement, definiteness, and the prior art.

The Examiner objected to the drawings for failure to comply with 37 C.F.R. § 1.821(d). Applicants have provided 17 new sheets of drawings for Figure 49, labeling the sheets of figures as 49A-Q. Applicants request that the objection be withdrawn.

Claims 6, 9-10, 13, and 24 were objected to as being in improper multiple dependent form. Applicants have amended these claims to remove improper multiple

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dependency and have added new claims 25-37 to include the subject matter cancelled from these claims. No new matter has been added by this amendment. Support for new claim 38 may be found in claim 2. Support for new claim 39 may be found in the specification on page 19, lines 21-26 and page 23, lines 16-23.

Written Description Rejection

The Examiner rejected claims 2, 4-6, 9-10, 13 and 24 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support in the specification. The Examiner is especially concerned about the limitation to claim 2 "fragment of extracellular or cytoplasmic P95/nucleolin." The Examiner argues that this phrase does not occur in the specification or the originally filed claims. The Examiner states that the application does not refer to the location of P95/nucleolin in the cell.

Applicants have reviewed the specification again and believe that it supports cell surface P95/nucleolin. Figure 22, provided on the face of the PCT published application, shows P95/nucleolin located on the extracellular side of the membrane of the cell. The P95/nucleolin depicted in this figure cannot be characterized as the nuclear nucleolin of the prior art.

Additionally, the context and general description of the invention focus on cell surface P95/nucleolin. The field of the invention section states that the invention relates to a new receptor for HIV retroviruses and the background states that HIV infects target cells by the fusion of viral and cellular membranes. (Specification, page 1). The receptor for HIV must necessarily be on the surface of the cell, and certainly cannot be

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present in the nucleus (as is discussed in the prior art). The specification continues by discussing the various cell surface proteins that are thought to be involved in HIV binding and entry into the cell.

The specification states on page 4, lines 13-15 that "[t]he inventors have also shown that the V3 loop peptide of the HIV1 Lai gp120 is able to bind to the same P95 protein at the cell surface." It describes the P95/nucleolin as "cell surface expressed" (page 5, lines 25-26), "present at the cell surface of a patient infected with human HIV retrovirus" (page 9, lines 24-25), and "located at the cell surface of the cell" (page 10, line 28).

Applicants have amended claim 2 to remove the objected to limitation and to include the limitation cell surface P95/nucleolin. Applicants thus request withdrawal of this rejection.

Definiteness Rejection

The Examiner also made a number of definiteness rejections to the claims. First the Examiner rejected claim 2 as containing several allegedly unclear phrases: "alters and/or prevents", "peptidic fragment", "homologous" and allegedly improper Markush language. Applicants have amended the claim to address several of these rejections.

In response to the Examiner's concerns regarding the term "homologous," Applicants have added the limitation that both the fragment and the pseudopeptide bind to HIV, in order to more fully describe what the inventors mean by homologous. The specification, page 16, as cited in the last response, and in conjunction with this new

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limitation, does define what the inventors mean by the term homologous. The cited section does state that the homologous polypeptides contain amino acid mutations that do not decrease the binding properties of the corresponding peptides to HIV and that both the original polypeptide and the homologous polypeptide (or in this case pseudopeptide) are able to bind to the V3 loop peptide or the gp120/gp125 proteins of HIV.

Applicants also add new claim 38, which is based on claim 2 but does not cover the pseudopeptide embodiments. Applicants request that the Examiner withdraw the definiteness rejections.

Novelty and Obviousness Rejection over *Callebaut*

The Examiner has maintained the rejection of claims 2, 4, 6, 9-10, 13, and 25 under 35 U.S.C. § 102(a) as anticipated by, or in the alternative under 35 U.S.C. § 103(a) as obvious over, *Callebaut*. The Examiner has previously argued that *Callebaut* discloses the use of pseudopeptides for inhibiting HIV entry (infection) by interfering with the binding between gp120 and the cellular receptor.

In the last response, Applicants argued that *Callebaut* only discloses the TASP pseudopeptide, and does not teach or suggest the use of peptidic fragments of extracellular or cytoplasmic (now cell surface) nucleolin or pseudopeptides homologous to them. Applicants also argued that this application does not claim the TASP pseudopeptide taught by *Callebaut*. In response, the Examiner states that the TASP

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pseudopeptide is encompassed by the instant invention since it is a pseudopeptide that has a function homologous to P95 nucleolin and/or a fragment thereof.

Applicants have already pointed the Examiner to the section of the specification that describes homology between proteins. The specification defines a homologous polypeptide as having one or several amino acid additions, deletions, and/or substitutions. Specification, page 16, lines 11-18. An unrelated protein cannot qualify as homologous under this definition.

The homologous pseudopeptide must have some sequence in common with the peptide fragment of the invention. The TASP pseudopeptide is structurally unrelated to the P95/nucleolin and thus cannot qualify as homologous. In fact, it binds to cell surface P95/nucleolin, blocking the interaction of this protein with HIV. (Specification, page 5, lines 23-26). Applicants request that the Examiner withdraw this rejection.

Thus, one of the characteristics of the claimed homologous molecules is that these molecules *bind to TASP pseudopeptides* described in *Callebaut*. The TASP pseudopeptides are not encompassed in the scope of the present invention.

Obviousness Rejection over *Srivastava*

The Examiner has also maintained the rejection of claims 2, 4-6, 9-10, 13 and 24 under 35 U.S.C. § 103(a) as obvious over *Srivastava*. In the last response, Applicants argued that the claims read on extracellular or cytoplamsic nucleolin, not the nuclear nucleolin described by *Srivastava*. The Examiner disagreed with this assessment,

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stating that because *Srivastava* isolated human nucleolin from the total RNA of the adrenal medulla all forms of nucleolin would be isolated.

Applicants, in response, have amended the claims to recite cell surface P95/nucleolin. As nuclear nucleolin is at least a component of the human nucleolin of *Srivastava*, if not the entire source of the nucleolin in that reference, the cell surface P95/nucleolin of the invention cannot be rendered obvious by *Srivastava*. Since the filing of this application, the inventors have shown that cell surface nucleolin is distinguishable from nuclear nucleolin. *See Hovanessian*, The Cell-Surface-Expressed Nucleolin is Associated with the Actin Cytoskeleton, Experimental Cell Research 261:312-328 (2000). This reference states that cell-surface nucleolin could be differentiated from that of the nucleus. *Id.* at 314-315. Applicants thus request that the Examiner withdraw this rejection.

Obviousness Rejection over *Rankin*

The Examiner has also maintained the rejection of claims 2, 4-6, 9-10, 13, and 24 under 35 U.S.C. § 103(a) as obvious over *Rankin*. In the last response, Applicants argued that *Rankin* teaches that nucleolin is a nucleolar specific protein that assists in the process of pre-ribosomal RNA as the ribosomes are assembled. Applicants also argued that the claims read on extracellular or cytoplasmic (now cell surface) nucleolin, not the nuclear nucleolin described in *Rankin*. The Examiner responds by stating that *Rankin* does not state that nucleolin is not a nucleolar specific protein that assists in the process of pre-ribosomal RNA as the ribosomes are assembled. The Examiner argues

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that *Rankin* merely speculates on a possible function of nucleolin. Additionally, the Examiner states that *Rankin* does not disclose the source of the nucleolin used to determine the cDNA sequence—and argues that it is not necessarily nuclear. Instead, the Examiner believes that *Rankin* uses a library constructed from total RNA.

Applicants have amended the claims to recite cell surface P95/nucleolin. As nuclear nucleolin is at least a component of the human nucleolin of *Rankin*, if not the entire source of the nucleolin in that reference, the cell surface P95/nucleolin of the invention cannot be rendered obvious by *Rankin*. Additionally, the Examiner cannot ignore *Rankin*'s plainly clear statement that "Nucleolin is a **nucleolar specific protein**" (emphasis added). Applicants request that the Examiner withdraw this rejection.

Conclusion

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing the claims in condition for allowance. Applicants submit that the proposed amendments of the claims do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Furthermore, Applicants respectfully point out that the final action by the Examiner presented some new arguments as to the application of the art against Applicant's invention. It is respectfully submitted that the entering of the Amendment

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would allow the Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: March 21, 2003

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APPENDIX TO THE AMENDMENT

2. (Twice Amended) An inhibitor molecule that alters [~~and/or prevents~~] the interaction between a receptor located on the surface of [~~an HIV infected~~] a cell and a gp120 envelope glycoprotein of a [~~said~~] HIV virus, wherein the inhibitor is chosen from at least one of:

a) a [~~peptidic~~] fragment of [~~extracellular or cytoplasmic~~] cell surface P95/nucleolin,

b) a [~~peptidic~~] fragment of P40/PHAPII,

c) a [~~peptidic~~] fragment of P30/PHAPI,

d) a pseudopeptide homologous to a [~~peptide~~] fragment of [~~extracellular or cytoplasmic~~] cell surface P95/nucleolin, wherein both the fragment and the pseudopeptide bind to HIV,

e) a pseudopeptide homologous to a [~~peptide~~] fragment of P40/PHAPII, wherein both the fragment and the pseudopeptide bind to HIV, and

f) a pseudopeptide homologous to a [~~peptide~~] fragment of P30/PHAPI, wherein both the fragment and the pseudopeptide bind to HIV.

4. (Twice Amended) An inhibitor molecule that is homologous to the inhibitor molecule of claim [~~3~~] 2, wherein said homologous inhibitor molecule comprises a peptide or pseudopeptide containing at least one amino acid addition, deletion, or substitution in the amino acid sequence compared to the inhibitor molecule of claim 2.

5. (Twice Amended) The inhibitor molecule according to any one of claims 2 [~~to~~] or 4 in which a -CONH- peptide bond is replaced by a ($-CH_2NH-$) reduced bond, a (-

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NHCO-) retro inverso bond, a (-CH_2-O-) methylene-oxy bond, a (-CH_2-S-) thiomethylene bond, a (-CH_2CH_2-) carba bond, a (-CO-CH_2-) cetomethylene bond, a (-CHOH-CH_2-) hydroxyethylene bond, a (-N-N-) bond, a E-alcene bond, or a (-CH=CH-) bond.

6. (Three Times Amended) The inhibitor molecule according to any one of claims 2 [~~to 5~~] or 4, which comprises an amino acid sequence chosen from:

- the sequence beginning at the amino acid in position 22 and ending at the amino acid in position 44 of SEQ ID NO: 22;

- the sequence beginning at the amino acid in position 143 and ending at the amino acid in position 171 of SEQ ID NO: 22;

- the sequence beginning at the amino acid in position 185 and ending at the amino acid in position 209 of SEQ ID NO: 22; and

- the sequence beginning at the amino acid in position 234 and ending at the amino acid in position 271 of SEQ ID NO: 22.

9. (Twice Amended) An inhibitor molecule, which comprises a polymer of an inhibitor molecule according to any one of [~~3 to 6~~] claim 2 or 4, that contains 2 to 20 monomer units from the amino acid sequence of P95/nucleolin, P40/PHAPIII, or P30/PHAPI.

10. (Twice Amended) The inhibitor molecule according to any one of claims 2 [~~to 6~~], 4 or 9, which is a MAP matrix structure.

13. (Three Times Amended) A composition comprising an inhibitor molecule according to any one of claims 2 [~~to 6 or 9 to 10~~] or 4, in combination with at least a second compound, wherein the second compound is an anti-HIV molecule.

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24. (Amended) A composition comprising an inhibitor molecule according to any one of claims 2[,] or 4[~~to 6, or 9 to 10~~], further comprising at least a second compound.

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